

CARDIOVASCULAR

Effect of low-dose ketamine on inflammatory response in off-pump coronary artery bypass graft surgery

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Background. Off-pump coronary artery bypass graft surgery (OPCAB) is still associated with a marked systemic inflammatory response. The aim of this study was to investigate whether pre-emptive, low dose of ketamine, which has been reported to have anti-inflammatory activity in on-pump coronary artery bypass surgery, could reduce inflammatory response in low-risk patients undergoing OPCAB.

Methods. In this prospective randomized-controlled trial, 50 patients with stable angina and preserved myocardial function undergoing OPCAB were randomly assigned to receive either 0.5 mg kg⁻¹ of ketamine (Ketamine group, *n*=25) or normal saline (Control group, *n*=25) during induction of anaesthesia. Inflammatory markers including C-reactive protein (CRP), interleukin (IL)-6, tumour necrosis factor- α (TNF- α), and cardiac enzymes were measured previous to induction (T1), 4 h after surgery (T2), and the first and second days after the surgery (T3 and T4).

Results. There were no significant intergroup differences in the serum concentrations of the CRP, IL-6, and TNF- α and cardiac enzymes. Pro-inflammatory markers and cardiac enzymes, except TNF- α , were all increased after the surgery compared with baseline values in both groups.

Conclusions. Low-dose ketamine administered during anaesthesia induction did not exert any evident anti-inflammatory effect in terms of reducing the serum concentrations of pro-inflammatory markers in low-risk patients undergoing OPCAB.

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In cardiac surgery, the degree of systemic inflammatory response is closely associated with patient's outcome.^{1–3} Considering that cardiopulmonary bypass (CPB) and the accompanied global myocardial ischaemia–reperfusion injury are the main inciting causes of this inflammatory response,⁴ off-pump coronary artery bypass graft surgery (OPCAB) would confer different impact on the degree of inflammatory reaction. Despite the theoretical advantage, however, OPCAB also elicits marked systemic inflammatory response,^{5, 6} even to a similar degree as in on-pump coronary artery bypass graft surgery (CABG).^{7–9} Inflammatory reaction, together with perturbation of the haemostatic prothrombotic system, might play a substantial role in developing adverse cardiovascular events in OPCAB.⁶ Therefore, therapeutic strategies to counteract the systemic inflammatory activation in OPCAB should be considered.

Ketamine is an i.v. anaesthetic agent demonstrating anti-inflammatory effect in various studies.^{10–12} Anti-inflammatory effect of low-dose ketamine has been demonstrated mainly as a significant reduction in the activity of pro-inflammatory mediators such as C-reactive protein (CRP) and interleukin (IL)-6 in cardiac surgery using CPB.^{11, 13} Thus, we evaluated whether low dose of ketamine administered during induction of anaesthesia could reduce the activity of pro-inflammatory mediators in low-risk patients undergoing OPCAB in a prospective, randomized and controlled trial.

Methods

After institutional review board approval and patients' consents, 50 patients undergoing elective, isolated multi-vessel OPCAB between March 2007 and August 2007

were studied. Patients were excluded, if they met one of the following criteria: age ≥ 75 yr, recent (<14 days) myocardial infarction, unstable angina with elevated creatine kinase-MB (CK-MB), elevated serum creatinine (>1.3 mg dl $^{-1}$) before operation, left ventricular ejection fraction (LVEF) $<40\%$, previous cardiac surgery, previous stroke or pulmonary disease, and history of treatment with steroid or non-steroidal anti-inflammatory drugs within a month. Emergency operations were also excluded.

Using a computer-generated randomization method, patients were randomly assigned to receive either a bolus of ketamine 0.5 mg kg $^{-1}$ (Ketamine group, $n=25$) or normal saline (Control group, $n=25$) during induction of anaesthesia. Being a double-blinded study, patients, anaesthetic provider, and anaesthetist collecting data were blinded to the study group, and ketamine or normal saline was prepared by an independent researcher in equal volumes in 10 ml syringes.

All preoperative medications except diuretics and antiplatelet agents were continued until the morning of surgery. Patients were premedicated with i.m. morphine 0.05–0.1 mg kg $^{-1}$ 1 h before anaesthesia. Upon arrival at the operating theatre, five ECG leads were attached, and leads II and V₅ were continuously monitored. A 20 G radial artery catheter was inserted to monitor arterial pressure. A thermodilution pulmonary artery catheter (Swan-Ganz CCombo® CCO/SvO₂; Edwards Lifesciences, Irvine, CA, USA) was inserted into the right internal jugular vein before induction of anaesthesia. Anaesthesia was induced with midazolam 0.03–0.05 mg kg $^{-1}$ after ketamine 1% (0.5 mg kg $^{-1}$) or the same volume of normal saline, according to randomization. After that, sufentanil 1.5–2.0 µg kg $^{-1}$ and rocuronium bromide 50 mg were administered and tracheal intubation was performed. Anaesthesia and neuromuscular block were maintained with sevoflurane (1.5–2.5%), and continuous infusion of sufentanil (0.2–0.3 µg kg $^{-1}$ h $^{-1}$) and vecuronium (1–2 µg kg $^{-1}$ min $^{-1}$). After induction of anaesthesia, a 7.0 MHz multiplane probe transoesophageal echocardiography was inserted to evaluate cardiac function. Rectal temperature was maintained above 36.0°C with forced warm air blanket, warm mattress, and fluid warmer, as necessary. Intravascular volume replacement was managed with crystalloid and colloid solutions to maintain pulmonary capillary wedge pressure between 8 and 16 mm Hg according to the baseline values. Norepinephrine (NE, 8 µg ml $^{-1}$) was infused when mean arterial pressure (MAP) or systolic arterial pressure decreased below 60 or 90 mm Hg, respectively. Neither corticosteroid nor antifibrinolytics were used in all patients.

All surgical procedures were performed by one surgeon (K.J. Yoo) through a median sternotomy and the heart was displaced using posterior pericardial stitch, large (12×70 cm) gauze swabs and was stabilized with tissue stabilizer (Octopus Tissue Stabilization System®, Medtronic Inc., USA). Intracoronary shunt (Shunt Florester®, Bio-Vascular, USA) was inserted during all grafting procedures of the left

anterior descending artery and distal right coronary artery. Grafting on other coronary branches was performed with proximal snare achieving temporary coronary haemostasis. During the period of heart displacement and grafting, MAP was maintained above 70 mm Hg with either 10–20° Trendelenburg position, NE infusion, or both. Intraoperative anticoagulation was achieved using 150 U kg $^{-1}$ of porcine heparin, with additional dosing administered to maintain activated clotting time above 300 s during anastomoses, and was reversed with protamine 0.5 mg per 150 U of heparin. A cell salvage device (Cell Saver®5+, Haemonetics, UK) was used in all cases and salvaged blood was re-infused to the patient before the end of the surgery. Allogenic packed red blood cells (pRBCs) were transfused when the haematocrit was $<25\%$ for patients ≥ 65 yr of age and when the haematocrit was $<22\%$ for patients <65 yr of age throughout the study period. Fresh frozen plasma or platelet concentrates were transfused when the INR was >1.5 or the platelet count $<50\,000$ mm $^{-3}$ after operation accompanied with excessive bleeding >200 ml h $^{-1}$ for 2 consecutive hours, respectively. All patients were transferred to the intensive care unit (ICU) after surgery.

CRP, IL-6, tumour necrosis factor- α (TNF- α), white blood cell (WBC) count, percentage of monocyte and neutrophil, troponin T (TnT), and CK-MB were measured before induction of anaesthesia (T0), 4 h after completion of anastomoses (T2), and on the first and second days after surgery (T3 and T4, respectively). Serum CRP was measured using rate immunonephelometry at the institutional laboratory. Low detection limit of this assay is 0.1 mg dl $^{-1}$ and the intra-assay and inter-assay precision coefficient of variations range were 3.5–11.1% and 4.0–12.1%, respectively. The samples for analysis of IL-6 and TNF- α were placed in ice after collection and then centrifuged immediately. Afterwards, the serum was separated and stored frozen at -70°C . IL-6 and TNF- α serum concentrations were assayed using enzyme-linked immunosorbent assay (Quantikine® high-sensitive immunoassay; R&D Systems, USA). The assay has a detection limit of 0.016 and 0.038 pg ml $^{-1}$ for IL-6 and TNF- α , respectively. The intra-assay and inter-assay precision coefficient of variations range for IL-6 were 6.9–7.4% and 6.5–9.6%, and those for TNF- α were 3.1–8.5% and 7.3–10.6%, respectively. All blood samples for biochemistry assays were obtained through the arterial line. Haemodynamic variables including heart rate, MAP, pulmonary arterial pressure, pulmonary capillary wedge pressure, central venous pressure, cardiac index, and right ventricular ejection fraction were recorded immediately before and after induction of anaesthesia (T0 and T1, respectively), T2, T3, and T4. The corresponding systemic and pulmonary vascular resistance indices were also calculated and recorded. The amount of NE infused during the surgery and the number of patients requiring inotropic agents, amount of salvaged blood, vasodilators, or NE infused after operation in the ICU was recorded. The amount of blood loss and transfusion, and fluid balance in

the operating theatre and ICU were recorded. Postoperative pain was controlled with i.v. patient-controlled analgesia with fentanyl in all patients. Additional use of rescue analgesics, time to extubation, duration of stay in ICU, and duration of postoperative hospitalization were recorded.

On the basis of our routine maximal CRP serum concentration after OPCAB [15 (SD 7) mg dl⁻¹] and the result of previous study that low dose of ketamine during induction of anaesthesia reduced CRP serum concentrations about 40–50% after operation compared with values in the control group,¹¹ a sample size of 22 in each group was determined with 90% power to detect a 7 mg dl⁻¹ difference in CRP serum concentration between the groups at an alpha level of 0.05 using independent *t*-test. In this study, 25 patients in each group were recruited for possible 10–15% dropouts during the study period. The study was discontinued in patients requiring partial aortic cross-clamp in which the surgeon routinely required infusion of solumedrol, conversion to on-pump CABG, haemodynamic instability requiring mechanical support, and reoperation.

Statistical analyses were performed using SPSS 14.0 (SPSS Inc., Chicago, IL, USA). Normality of distribution was assessed with the q–q plot and the Shapiro–Wilk test. Parametric data were analysed using the independent *t*-test and repeated measures ANOVA followed by *post hoc* Dunnett's test. Non-parametric data were compared using the Wilcoxon rank-sum test for between the groups and Friedman's test for within the groups. Where a difference was indicated by Friedman's test, this was further investigated by Mann–Whitney test with the Bonferroni correction of the resulting *P*-values. Statistical differences between the groups were evaluated by χ^2 test or by Fisher's exact test when appropriate. All values were expressed as median (range), mean (SD), or the number of patients. A *P*-value of <0.05 was considered as statistically significant.

Results

All patients enrolled in this study underwent OPCAB successfully. Patients' characteristics were similar between the groups (Table 1). The amount of midazolam and sufentanil administered during induction of anaesthesia was similar between the Control and the Ketamine groups [2.9 (0.7) vs 3.8 (3.4) mg and 96 (32) vs 100 (26) µg, respectively] (*P*=0.459 and 0.773, respectively). Duration of surgery, number of grafts and total graft reconstruction time, and amount of NE infused, salvaged blood, transfusion, and fluid balance in the operating theatre were similar between the groups (Table 2).

There were no significant differences in the pro-inflammatory markers' serum concentrations and cardiac enzyme concentrations between the groups throughout the study period. CRP increased significantly compared with the baseline value in both groups throughout the postoperative period. IL-6 was highest at T2 and decreased as

Table 1 Patients' characteristics. Data are mean (range), mean (SD) or number of patients. LVEF, left ventricular ejection fraction; ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers

Factors	Control group (n=25)	Ketamine group (n=25)
Age (yr)	64 (50–74)	61 (50–73)
Sex (M/F)	16/9	18/7
Body surface area (m ²)	1.7 (0.2)	1.7 (0.2)
LVEF (%)	62.6 (6.7)	62.4 (7.3)
Hypertension	16	17
Diabetes	8	14
Preoperative medication		
Calcium channel blocker	12	17
β-blockers	19	17
ACE inhibitors	4	7
ARBs	8	4
Statins	17	23

Table 2 Intraoperative parameters. Data are mean (SD), median (range), or number of patients. NE, norepinephrine; pRBC, packed red blood cell

Factors	Control (n=25)	Ketamine (n=25)	<i>P</i> -value
Duration of surgery (min)	243 (43)	250 (46)	0.550
Number of grafts per patient	3.5 (0.6)	3.3 (0.6)	0.230
Total graft reconstruction time (min)	35 (9)	33 (9)	0.609
Amount of infused NE (µg)	230 (166)	203 (160)	0.581
Amount of salvaged blood (ml)	259 (164)	195 (100)	0.105
Amount of transfused pRBC (ml)	0 (0–750)	0 (0–500)	0.704
Patients transfused with pRBC	9	10	1.000
Amount of i.v. fluid (ml)			
Colloid	1291 (252)	1308 (244)	0.835
Crystalloid	3249 (1187)	2675 (892)	0.142

time passed after surgery but still higher than the baseline value in both groups at T4. TNF-α was not significantly changed in both groups throughout the perioperative period. The percentage of monocyte decreased significantly compared with the baseline value in both groups throughout the postoperative period. WBC count, the percentage of neutrophil, TnT, and CK-MB significantly increased compared with the baseline values throughout the postoperative period in both groups (Fig. 1).

Haemodynamic variables were similar between the groups (data are not shown). Postoperative data are demonstrated in Table 3. The number of patients requiring cardiotoxic agents was similar between the groups. The frequency of treatment with rescue analgesics, time to extubation, and duration of stay in the ICU and postoperative hospitalization were also similar between the groups. One patient in each group developed elevation of serum creatinine concentration (>2.0 mg dl⁻¹) after operation and recovered within 1 week. There were no major complications including major stroke, renal failure requiring dialysis, cardiac reoperation, prolonged ventilation more than 48 h, and deep sternal wound infection.

Discussion

This is the first study investigating the anti-inflammatory effect of low dose of ketamine in low-risk patients

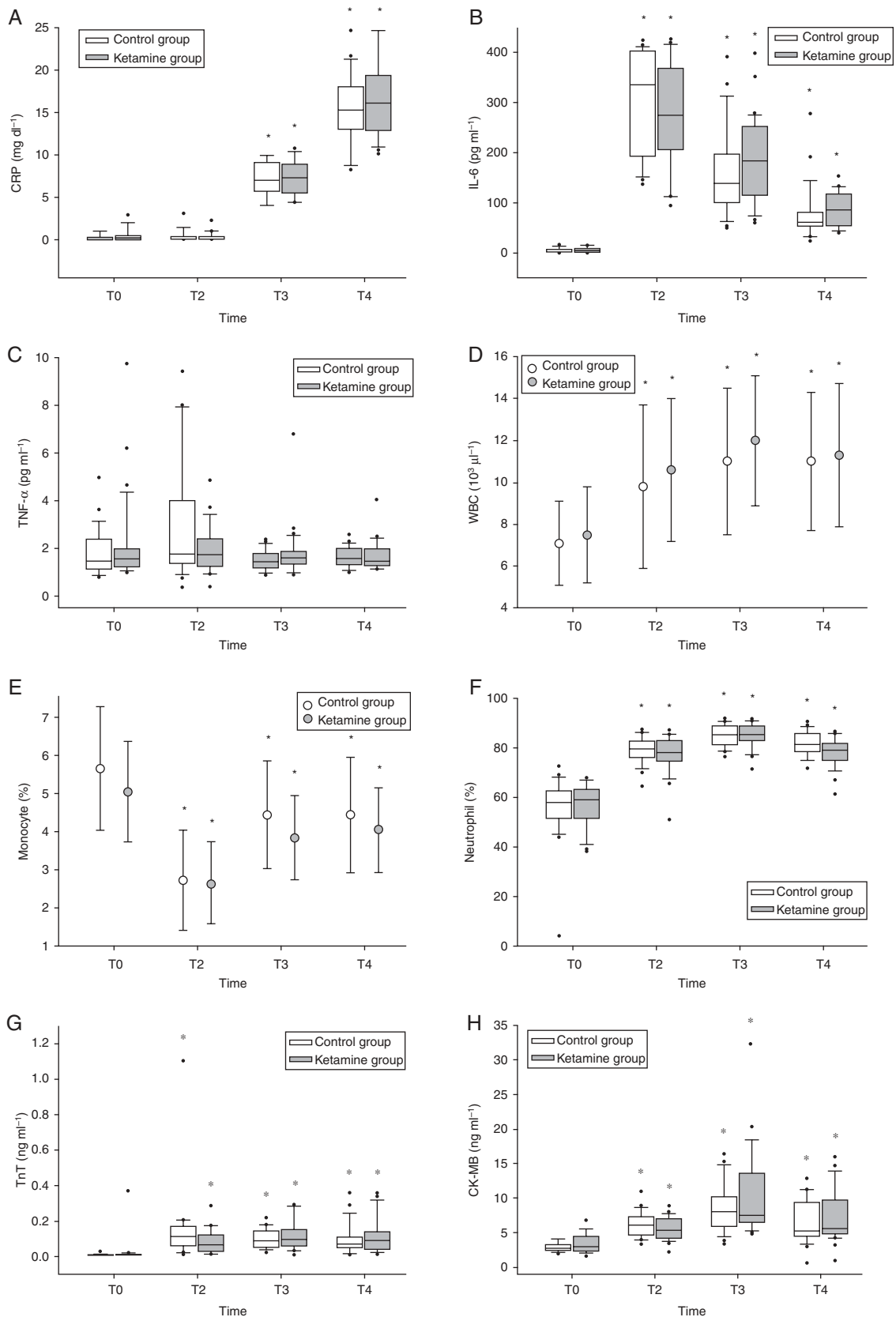


Fig 1 Changes in biological markers. (A) Changes in CRP, (B) IL-6, (C) TNF-α, (D) WBC count, (E) monocyte, (F) neutrophil, (G) TnT, and (H) CK-MB. Data are expressed as median (min, max) or mean (sd). T0, pre-induction; T2, 4 h after grafting completion; T3, postoperative 1 day; T4, postoperative 2 day. **P* < 0.05 compared with values at T0.

Table 3 Postoperative data. Data are mean (SD), median (range), or number of patients. Cr, creatinine; pRBC, packed red blood cell; ICU, intensive care unit

Factors	Control (n=25)	Ketamine (n=25)	P-value
Patients treated with			
Norepinephrine	15	20	0.217
Nicardipine	16	12	0.393
Nitroprusside	8	8	1.000
Milrinone	1	4	0.349
Frequency of additive analgesics	2.5 (2.0)	2.6 (4.2)	0.932
Patients with Cr >2.0 mg dl ⁻¹	1	1	1.000
Amount of transfused pRBC (ml)	0 (0–1120)	0 (0–1000)	0.647
Patients transfused with pRBC	7	9	0.762
Amount of i.v. fluid (ml)			
Colloid	77 (123)	122 (154)	0.257
Crystalloid	1543 (629)	1574 (485)	0.847
Time to extubation (min)	831 (234)	875 (251)	0.570
ICU day (day)	3.0 (0.7)	3.0 (0.4)	1.000
Hospital day (day)	14.4 (2.9)	13.2 (4.0)	0.212

undergoing OPCAB. No significant effect of ketamine on pro-inflammatory markers' serum concentrations including CRP, IL-6, and TNF- α was observed unlike in previous studies with on-pump CABG.^{11 12}

Since CPB has been recognized as the main cause of inflammatory activation,⁴ OPCAB has been expected to protect patients from complications of systemic inflammatory response. Studies, however, have presented that performing OPCAB may result in reduction, but not in elimination, of the inflammatory response.^{8 14} Some inflammatory markers such as IL-6, IL-8, IL-2R, and CRP were similarly and significantly activated both in OPCAB and in on-pump CABG.⁹ Regarding those results and the strong association of the inflammatory markers with prognosis,^{1–3} clinical approaches aimed at reducing perioperative inflammatory response might be beneficial in improving patient's outcome after OPCAB.

Ketamine is a non-competitive *N*-methyl-D-aspartate receptor antagonist, and in addition to its anaesthetic activity, the positive immunomodulatory effect of ketamine deserves special interest in the case of septic or cardiac surgical patient.¹⁵ Anti-inflammatory effects of ketamine are thought to be mediated through inhibition of nuclear factor (NF)- κ B, which regulates the transcription of genes that encode the production of pro-inflammatory cytokines.¹⁶ Indeed, anti-inflammatory effect of ketamine has been well demonstrated mainly in terms of reducing the activity of pro-inflammatory mediators, such as CRP, IL-6, and TNF- α , in most studies.^{11 17–20} Even a small dose of ketamine administered during induction of anaesthesia significantly attenuated the increase in IL-6 and CRP in cardiac surgical patients undergoing CPB.¹¹ Therefore, to assess the anti-inflammatory effects of ketamine in OPCAB, we measured CRP, IL-6, and TNF- α , which are all well-established markers of systemic inflammation. In the current trial, ketamine did not significantly affect the pro-inflammatory mediators' serum concentrations and leucocyte counts.

As this is the first study investigating anti-inflammatory effects of ketamine in OPCAB, reasons for the discrepancies between the current data and those of the previous studies in on-pump CABG^{11 12} are difficult to elucidate. In addition, other factors possibly affecting the perioperative inflammatory response such as preoperative medications, history of diabetes mellitus, perioperative transfusion, and fluid balance were not clarified in the previous studies addressing the anti-inflammatory effects of ketamine,^{11 12} whereas those factors were prospectively controlled and similar between the groups in this study. Despite these factors, proposed explanations for the observed lack of anti-inflammatory effects of ketamine in this study are as follows. First, considering that the protective anti-inflammatory effect of ketamine was presented to be different according to the degree of injury and inflammatory activation,²¹ less activation of inflammatory reaction after OPCAB would be the most responsible cause for the distinguished result of the current study. Furthermore, to avoid the introduction of confounders, we had only enrolled low-risk patients with preserved LVEF and stable angina, thus the observed activation of innate immunity with its pro-inflammatory markers seems to be controlled or adaptive. Indeed, the increase in CRP and TNF- α concentration in this study was notably lower in both groups than those of previous studies.^{8 11 22 23} Secondly, differences in anaesthetic agents could also have contributed to the results. In contrast to the previous studies in which fentanyl was the main anaesthetic agent, sevoflurane was the main anaesthetic agent in this study. Volatile anaesthetics have dose-dependent inhibitory effects on neutrophil functions and suppress cytokine release in contrast to synthetic opioid which has minimal effects on immunity.²⁴ Thirdly, most of the patients were on statin therapy before the surgery in this study, which has been reported to exert significant anti-inflammatory effects in cardiac surgical patients.²⁵ Although there is currently no evidence regarding the anti-inflammatory effects of statin in OPCAB and the number of patients treated with statin was similar between the groups, the resultant attenuation and modification of the overall inflammatory activity could have contributed to the observed lack of anti-inflammatory effect of ketamine in this study.

The dose of ketamine in this study was decided according to the report that 0.5 mg kg⁻¹ of ketamine attenuated increase in CRP and IL-6 after CPB.¹¹ Since anti-inflammatory effect of ketamine is dose-related,²⁶ higher dose of ketamine could have attenuated inflammatory reactions in OPCAB. It should be considered that a larger dose of ketamine can elicit adverse haemodynamic modifications towards an increase in myocardial oxygen consumption,²⁷ since ketamine produces a dose-related increase in cardiovascular stimulation.

The limitation of this study is as follows. We did not assess anti-inflammatory mediators such as IL-10, which also has been presented to block the activity of NF- κ B,²⁸

therefore could not assess any effects of ketamine on the anti-inflammatory mediators. Conflicting results have been reported regarding the ketamine's effect on the anti-inflammatory mediators, and although low-dose ketamine was reported to attenuate increases in IL-10 in OPCAB,¹¹ other studies have failed to demonstrate any effects on the anti-inflammatory mediators.^{29,30}

In conclusion, low dose of ketamine administered during induction of anaesthesia could not reduce CRP, IL-6, and TNF- α serum concentration in low-risk patients undergoing OPCAB.

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